

Remarks

Applicant respectfully requests consideration of the remarks provided herein. Claims 29, 32, and 34-39 have been canceled and claims 1, 30, 31, 33, 63, and 71 have been amended. Accordingly, claims 1-28, 30-31, 33, 40-42 and 47-71 are pending.

The Examiner rejected claims 1-42, 47-48, 51 and 58-71 under 35 USC § 103(a) as unpatentable over WO 99/13816 by itself. This rejection is respectfully traversed.

Independent claims 1, 63, and 71 recite a pharmaceutical agent selected from an anthracycline chemotherapeutic agent, an anthracenedione, and a vinca alkaloid.

At page 2 of the Office action, the Examiner acknowledges that WO 99/13816 does not teach the loading of active agents other than camptothecins. The Examiner goes on to conclude that it "would have been obvious to one of ordinary skill in the art to load any agent since the principle of loading is the same." The Examiner has not identified any support for this conclusion in WO 99/13816. Accordingly, Applicant submits that the Examiner is taking "official notice." If the Office maintains the rejection over WO 99/13816 alone, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support this finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that that loading the recited a pharmaceutical agent selected from an anthracycline chemotherapeutic agent, an anthracenedione, and a vinca alkaloid was obvious.

Since the Examiner has failed to properly support the rejection of claims 1-42, 47-48, 51 and 58-71 under 35 USC § 103(a) over WO 99/13816 alone, withdrawal of the rejection is appropriate and is requested.

The Examiner rejected claims 1-42, 47-48, 51 and 58-71 under 35 USC § 103(a) as being unpatentable over WO 99/13816 in combination with EP 0 719 546.

Independent claims 1, 63, and 71 recite the following:

(a) contacting liposomes in an aqueous solution of at least about 60 mM of an acid with a pharmaceutical agent selected from an anthracycline chemotherapeutic agent, an

anthracenedione, and a vinca alkaloid, at a temperature wherein the protonated form of the pharmaceutical agent is charged and is not capable of permeating the membrane of the liposomes, and wherein the unprotonated form of the pharmaceutical agent is uncharged and is capable of permeating the membrane of the liposomes;

(b) actively loading the liposomes with the pharmaceutical agent by raising the pH of the solution to 5.0 or above;

(c) cooling the solution to a temperature at which the unprotonated form of the pharmaceutical agent is not capable of permeating the membrane of the liposomes; and

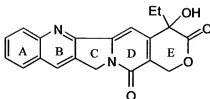
(d) contacting the solution with a weak base that is an ammonium salt or an alkyl amine, in an amount effective to raise the pH of the internal liposome to provide gradient loaded liposomes

WO 99/13816 discusses methods for loading liposomes with camptothecins.

EP 0 719 546 discusses gradient loading of liposomes – however, EP 0 719 546 does not disclose a process that includes steps c and d above. Additionally, EP does not discuss loading any camptothecin compounds.

In order to make a rejection under 35 U.S.C. 103(a) the Examiner first must establish a *prima facie* case of obviousness. Three criteria must be met: 1) there must be some suggestion or motivation, either in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not be based on applicants disclosure. M.P.E.P. 2142.

The Examiner has not provided any explanation regarding why one skilled in the art would have had a reasonable expectation that the disclosure of WO 99/13816 could have been combined with the disclosure of EP 0 719 546 as suggested by the Examiner. The camptothecins discussed in WO 99/13816 comprise the following ring system, wherein the lactone ring E can be open or closed (please see WO 99/13816 at pages 8-10):



These camptothecin compounds differ significantly in chemical structure from the agents that were loaded in EP 0 719 546. The camptothecin compounds also have significantly different physical properties (e.g. molecular weights, melting points, lipophilicities, solubilities, etc.) from the pharmaceutical agents recited in the instant claims. Because the camptothecins discussed in WO99/13816 differ significantly from the compounds discussed in EP 0 719 546, it is respectfully submitted that one skilled in the art would not have had a reasonable expectation that that compounds discussed in EP 0 719 546 would be operative in the loading methods discussed WO 99/13816. This is especially true, since the loading process discussed in EP 0 719 546 does not include steps c and d recited in the claims. Accordingly, the Examiner has not established that the instant claims are *prima facie* obvious over WO 99/13816 in combination with EP 0 719 546. Withdrawal of the rejection is appropriate and is requested.

Additionally, it is submitted that the Examiner has not provided any evidence to support his conclusion that one of ordinary skill in the art would be motivated to load any active agent in WO 99/13816 since EP 0 719 546, which uses a similar loading procedure, teaches that several active agents could be loaded using a pH method (Office action at page 2 bridging to page 3). As discussed above, there are significant differences between the agents discussed in the two cited documents. Accordingly, Applicant submits that the Examiner is taking "official notice" that one of ordinary skill in the art would be motivated to load any active agent in WO 99/13816. If the Office maintains the rejection over WO 99/13816 in combination with EP 0 719 546, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support this finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that one of ordinary skill in the art would be motivated to load any active agent in WO 99/13816.

The Examiner also rejected claims 7 and 49 under 35 USC § 103(a) as being unpatentable over WO 99/13816 by itself or in combination with EP 0 719 546, further in view of Webb (5,814,335) of record. This rejection is respectfully traversed.

At page 4 of the office action the Examiner stated that what is lacking in EP 0 719 546 and WO 99/13816 is the use of sphingomyelin as a liposome forming lipid. As discussed above, the independent claims 1, 63, and 71 are not obvious over WO 99/13816 taken alone or in combination with EP 0 719 546. It is respectfully submitted that the Examiner has not suggested that the secondary document Webb cures the deficiencies in the other documents discussed above, since Webb was only cited with respect to sphingomyelin as a liposome forming lipid. Accordingly, the instant claims are not obvious over the disclosure of WO 99/13816 taken alone or in combination with EP 0 719 546, further in view of Webb (5,814,335). Withdrawal of this rejection is appropriate and is respectfully requested.

Additionally, the Examiner is requested to confirm that claim 49 was intentionally included in this rejection. Claim 49 does not recite sphingomyelin, so it is not clear why it was included in this rejection.

The Examiner has also rejected claims 52-57 under 35 USC § 103(a) as being unpatentable over WO 99/13816 by itself or in combination with EP 0 719 546, further in view of Clerc (5,939,096). This rejection is respectfully traversed.

At page 5 of the Office action the Examiner stated that what is lacking in EP 0 719 546 and WO 99/13816 is the teaching of dehydrating the liposomes in the presence of cryoprotectants. As discussed above, the independent claims 1, 63, and 71 are not obvious over WO 99/13816 taken alone or in combination with EP 0 719 546. It is respectfully submitted that the Examiner has not suggested that the secondary document Clerc cures the deficiencies in the other documents discussed above, since it was only cited with respect to dehydrating the liposomes in the presence of cryoprotectants. Accordingly, the instant claims are not obvious over the disclosures of WO 99/13816 taken alone or in combination with EP 0 719 546, further in view of Clerc (5,939,096). Withdrawal of this rejection is respectfully requested.

The Examiner has provisionally rejected claims 1-42 and 47-71 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-71 of copending Application No. 10/723,610.

Claim amendments will be submitted shortly in co-pending Application No. 10/723,610. Accordingly, the propriety of the double patenting rejection can not be properly assessed at this time. Applicant will address any double patenting issues once otherwise allowable subject matter has been identified in both pending applications. Applicant thanks the Examiner for pointing out this potential issue.

The Examiner has also rejected claims 1-42 and 47-71 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 30-31 of U.S. Patent No. 6,740,335 by itself or in combination with EP cited above. This rejection is respectfully traversed.

US 6,740,335 is related to WO 99/13816. In the instant Office action, the Examiner rejected the pending claims under 35 USC 103(a) as obvious over WO 99/13816 taken alone or in combination with EP 0 719 546 (see above). It is respectfully submitted that the instant claims are non-obvious over the claims of US 6,740,335 either alone or in combination with EP 0 719 546 for the reasons presented above with respect to the rejection under 35 USC 103(a) over WO 99/13816 taken alone or in combination with EP 0 719 546. Accordingly, withdrawal of the obviousness type double patenting rejection over claims 30-31 of US Patent 6,740,335 alone or in combination with EP 0 719 546 is appropriate and is requested.

Finally, the Examiner is requested to confirm the status of claims 49 and 50. These claims were not included in the rejection under 35 USC § 103(a) over WO 99/13816 alone or in combination with EP 0 719 546. Accordingly, the only outstanding rejection for claim 50 is the statutory obviousness-type double patenting rejection over claims 30-31 of U.S. Patent No. 6,740,335 by itself or in combination with EP 0 719 546; the only outstanding rejections for claim 49 are the statutory obviousness-type double patenting rejection over claims 30-31 of U.S. Patent No. 6,740,335 by itself or in combination with EP 0 719 546, and the rejection under 35 USC § 103(a) as being unpatentable over WO 99/13816 by itself or in combination with EP 0 719 546, further in view of Webb (5,814,335), which rejection is believed to have been made inadvertently (please see above).

CONCLUSION

In light of the amendments and remarks provided herein, it is respectfully submitted that claims 1-28, 30-31, 33, 40-42 and 47-71 are in condition for allowance. The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

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By their Representatives,

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